Medical Policy
Quantitative Assay for Measurement of HER2 Total Protein Expression and HER2 Dimers

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Policy Number: 397
BCBSA Reference Number: 2.04.76

Related Policies
None

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO BlueSM and Medicare PPO BlueSM Members

The assessment of HER2 status by quantitative total HER2 protein expression and HER2 homodimer measurement is considered INVESTIGATIONAL.

Medicare HMO BlueSM and Medicare PPO BlueSM Members

Prior Authorization Information
Pre-service approval is required for all inpatient services for all products.
See below for situations where prior authorization may be required or may not be required.
Yes indicates that prior authorization is required.
No indicates that prior authorization is not required.
N/A indicates that this service is primarily performed in an inpatient setting.

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<td><strong>Outpatient</strong></td>
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<td>Medicare HMO BlueSM</td>
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<td>Medicare PPO BlueSM</td>
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CPT Codes / HCPCS Codes / ICD Codes
Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.
Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

CPT Codes
There is no specific CPT code for this testing.

Description
The HER-family of receptor tyrosine kinases (EGFR/HER1, ErbB2/HER2, ErbB3/HER3, and ErbB4/HER4) plays a major role in the pathogenesis of many solid tumors. In approximately 25-30% of breast cancers, overexpression of HER2 has been linked to shorter disease-free (DFS) and overall survival (OS), lack of responsiveness to tamoxifen antiestrogen therapy and altered responsiveness to a variety of cytotoxic chemotherapy regimens.

Trastuzumab, a monoclonal antibody directed at the extracellular domain of HER2 has offered significant DFS and OS advantages in the metastatic and adjuvant settings in HER2-overexpressing patients, although not all patients respond. Fewer than 50% of patients with metastatic HER2-positive breast cancer show initial benefit from trastuzumab treatment, and many of those eventually develop resistance.

Current methodologies for the selection of HER2-positive patients include immunohistochemistry (IHC) to detect HER2 protein overexpression, and fluorescence in situ hybridization (FISH) to detect HER2 gene amplification. However, controversy still exists regarding the accuracy, reliability, and interobserver variability of these assay methods. IHC provides a semiquantitative measure of protein levels (scored as 0, 1+, 2+, and 3+) and the interpretation may be subjective. FISH is a quantitative measurement of gene amplification, in which the HER2 gene copy number is counted. However, FISH, which is considered to be more quantitative analytically, is not always representative of protein expression, and multiple studies have failed to demonstrate a relationship between HER2 gene copy number and response to trastuzumab.

Whereas patients who overexpress HER2 protein (IHC) or show evidence of HER2 gene amplification (FISH) have been shown to experience better outcomes on trastuzumab than those scored negative by those assays, differences in the degree of expression or amplification by these methods have generally not been shown to discriminate between groups with different outcomes. IHC and FISH testing may be affected by interlaboratory variability, and neither test provides quantitative data that reflect the activation state of signaling pathways in tumors, which may limit their utility in patient selection.

Most laboratories in North America and Europe use IHC to determine HER2 protein status, with equivocal category results (2+) confirmed by FISH (or more recently by chromogenic in situ hybridization [CISH]).

Normally, HER2 activates signaling pathways by dimerizing with ligand-bound EGFR-family members such as HER1 and HER3. A HER2 ligand has not been identified, but overexpressed HER2 is constitutively active. When HER2 is pathologically overexpressed, the receptor may homodimerize and activate signaling cascades in the absence of the normal regulatory control imposed by the requirement for ligand binding of its heterodimerization partners.

A novel assay (HERmark® Breast Cancer Assay; Monogram Biosciences, South San Francisco, CA) was developed to quantify total HER2 protein expression (H2T) and HER2 homodimers (H2D) in formalin-fixed, paraffin-embedded (FFPE) tissue samples.

Summary
Novel assays that quantitatively measure total HER2 protein expression and homodimers have been developed in an effort to improve the accuracy and consistency of HER2 testing.

Retrospective analyses using HERmark® have shown that the assay may predict a worse response to trastuzumab in certain populations. However, findings are inconsistent, and no clear association with
clinical outcomes has been shown. Additionally, cut points for defining patient groups varied across studies. Clinical utility of the HERmark® assay has not been demonstrated, and clinical trials are needed to determine the impact on clinical outcomes of patients stratified by the HERmark® assay.

Policy History

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<th>Date</th>
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<tr>
<td>6/2015</td>
<td>Local Coverage Determination (LCD): Molecular Diagnostic Tests (MDT) (L33541) added.</td>
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<td>12/2014</td>
<td>New references added from BCBSA National medical policy.</td>
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<td>9/2014</td>
<td>Clarified coding information.</td>
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<td>11/1/12</td>
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Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:
- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines

References